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A Randomized Trial Comparing Antibiotics with Appendectomy for Appendicitis

The CODA Collaborative*

ABSTRACT

BACKGROUND

Antibiotic therapy has been proposed as an alternative to surgery for the treatment of appendicitis.

METHODS

We conducted a pragmatic, nonblinded, noninferiority, randomized trial comparing antibiotic therapy (10-day course) with appendectomy in patients with appendicitis at 25 U.S. centers. The primary outcome was 30-day health status, as assessed with the European Quality of Life–5 Dimensions (EQ-5D) questionnaire (scores range from 0 to 1, with higher scores indicating better health status; noninferiority margin, 0.05 points). Secondary outcomes included appendectomy in the antibiotics group and complications through 90 days; analyses were prespecified in subgroups defined according to the presence or absence of an appendicolith.

RESULTS

In total, 1552 adults (414 with an appendicolith) underwent randomization; 776 were assigned to receive antibiotics (47% of whom were not hospitalized for the index treatment) and 776 to undergo appendectomy (96% of whom underwent a laparoscopic procedure). Antibiotics were noninferior to appendectomy on the basis of 30-day EQ-5D scores (mean difference, 0.01 points; 95% confidence interval [CI], −0.001 to 0.03). In the antibiotics group, 29% had undergone appendectomy by 90 days, including 41% of those with an appendicolith and 25% of those without an appendicolith. Complications were more common in the antibiotics group than in the appendectomy group (8.1 vs. 3.5 per 100 participants; rate ratio, 2.28; 95% CI, 1.30 to 3.98); the higher rate in the antibiotics group could be attributed to those with an appendicolith (20.2 vs. 3.6 per 100 participants; rate ratio, 5.69; 95% CI, 2.11 to 15.38) and not to those without an appendicolith (3.7 vs. 3.5 per 100 participants; rate ratio, 1.05; 95% CI, 0.45 to 2.43). The rate of serious adverse events was 4.0 per 100 participants in the antibiotics group and 3.0 per 100 participants in the appendectomy group (rate ratio, 1.29; 95% CI, 0.67 to 2.50).

CONCLUSIONS

For the treatment of appendicitis, antibiotics were noninferior to appendectomy on the basis of results of a standard health-status measure. In the antibiotics group, nearly 3 in 10 participants had undergone appendectomy by 90 days. Participants with an appendicolith were at a higher risk for appendectomy and for complications than those without an appendicolith. (Funded by the Patient-Centered Outcomes Research Institute; CODA ClinicalTrials.gov number, NCT02800785.)

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Appendectomy has long been the standard treatment for appendicitis, even though successful use of antibiotic therapy as an alternative was reported more than 60 years ago.[1] Although there have been several randomized trials of antibiotics for appendicitis in adults,[2-7] exclusion of important subgroups (in particular, patients with an appendicolith, who may be at an increased risk for complications), small sample sizes, and questions about applicability to the general population have limited the use of this treatment.[8] As recently as 2014, more than 95% of U.S. patients with appendicitis underwent appendectomy.[9] However, with the pandemic of coronavirus disease 2019 (Covid-19), health systems and professional societies such as the American College of Surgeons[10] have suggested reconsideration of many aspects of care delivery, including the role of antibiotics in the treatment of appendicitis.

We conducted the Comparison of Outcomes of Antibiotic Drugs and Appendectomy (CODA) trial to compare antibiotic therapy with appendectomy in adults with appendicitis, including those with an appendicolith. The trial design was based on recognition that not all patients prioritize the multiple outcomes related to appendicitis care in the same way. An overall measure of health status was used for the primary outcome, and analyses of several secondary clinical and patient-reported outcomes, complications, and time spent in health care settings were performed. We had initially planned to report the results after all the participants had at least 1 year of follow-up, but given the Covid-19–related interest in the management of appendicitis, we describe results based on the first 90 days after randomization.

Methods

Trial Design and Oversight

The CODA trial was funded by the Patient-Centered Outcomes Research Institute. The trial design has been described previously,[11] and the protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org. The trial was designed with the engagement of patient stakeholders[12,13] to identify outcomes that they considered to be most important.[14] Institutional review boards at 25 clinical sites participating in the University of Washington–based Comparative Effectiveness Research Translation Network[15] approved the protocol, and the participants provided written informed consent. The authors vouch for the completeness and accuracy of the data and the fidelity of the trial to the protocol.

Trial Population

Consecutive English- or Spanish-speaking adults (≥18 years of age) in emergency departments who had appendicitis that had been confirmed on imaging were approached by research coordinators. On the basis of a previous trial[6] suggesting that patients with an appendicolith had an increased risk of complicated appendicitis, patients with evidence of an appendicolith on imaging were included in a prespecified subgroup. Patients were excluded from the trial if they had septic shock, diffuse peritonitis, recurrent appendicitis, evidence of severe phlegmon on imaging (if the surgeon determined that a more extensive operation, such as ileocolectomy, was likely to be performed), walled-off abscess, free air or more than minimal free fluid, or evidence suggestive of neoplasm. Other exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org. In the absence of these conditions, evidence of perforation on imaging was not an exclusion criterion. Sites were regularly audited to confirm that all patients with appendicitis were screened. The consent process included a standardized informational video (or pamphlet) in English (https://youtu.be/EQ8Iyc4_55k) or Spanish (https://youtu.be/5kTdVoq0GZ4). Consenting participants were randomly assigned to a treatment group by the data coordinating center. Randomization was performed with the use of permuted blocks (random block sizes of 4, 6, and 8) and was stratified according to recruitment site and appendicolith status (present or absent). Those who declined to undergo randomization were invited to participate in an observational cohort study.[11]

Treatments

Participants who were randomly assigned to the antibiotics group received an intravenous formulation for at least 24 hours, followed by pills, for a 10-day total course. Clinical teams selected antibiotics from Surgical Infection Society and

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Infectious Diseases Society of America guidelines for intraabdominal infections (Fig. S1 in the Supplementary Appendix).[16,17] Participants were either hospitalized for the administration of intravenous antibiotics or were discharged from the emergency department after they had received intravenous antibiotics for 24 hours or with 24 hours of bioavailability. Standard discharge criteria included intake of liquids without difficulty, adequate pain control, and an improving clinical condition. Appendectomy was recommended if diffuse peritonitis or septic shock developed at any time or if worsening signs and symptoms developed after 48 hours of antibiotics; however, these criteria were not required to be met. In the absence of these conditions, participants were encouraged to continue taking antibiotics, and the decision to perform appendectomy was ultimately made by the treating clinician. The protocol did not specify how to manage recurrent appendicitis or symptoms or how to address patients' appendix-related concerns. In participants who were randomly assigned to the appendectomy group, laparoscopic and conventional (open) surgical approaches were allowed; the technique was not standardized. Usual preoperative and postoperative care and discharge criteria were used.

The amount of analgesic agents or pain-control medications provided was not standardized or monitored in either treatment group. In both groups, the protocol allowed for crossover on the basis of participant and clinician decision making.

OUTCOMES AND MEASURES

The primary outcome was 30-day health status, as assessed with the use of the European Quality of Life–5 Dimensions (EQ-5D) questionnaire[18] (scores range from 0 to 1, with higher scores indicating better health status; minimal clinically important difference, 0.05 points[19]; https://euroqol.org). Participants were to be contacted at 24 hours after discharge and surveyed by telephone, mail, or email at 1, 2, and 4 weeks, quarterly for a year, and then yearly. Secondary outcomes included patient-reported resolution of symptoms, which was defined as the absence of pain, tenderness, and fever; serious adverse events; National Surgical Quality Improvement Program (NSQIP)–defined complications at the time of the index treatment or during follow-up,[20] including site-related infectious complications (defined as incisional infections or organ–space infections [abscesses]), specifically those that led to percutaneous drainage procedures; reactions to antibiotics that led to a health care encounter; *Clostridioides difficile* infections; more extensive procedures (e.g., small-bowel or colon resection, reoperation, laparotomy, colostomy, or ileostomy); appendiceal perforation found during an operation or on pathological review; appendiceal neoplasm; and appendectomy in the antibiotics group (Table S1). Visits to the emergency department or urgent care clinic for related symptoms, days in the emergency department or hospital related to appendicitis symptoms or treatment-related complications, and days of missed work for the participant and the caregiver were recorded. Serious adverse events were adjudicated by an independent safety monitor to confirm severity and relatedness to treatment.

STATISTICAL ANALYSIS

Under the assumption of a mean (±SD) score on the EQ-5D of 0.90±0.12 after treatment for appendicitis,[21] we calculated that a sample of 1552 participants would give the trial sufficient power (>82%) to rule out a between-group difference in the EQ-5D score as small as 0.05 points, on the basis of follow-up data for 90% of the participants at 30 days. Within an intention-to-treat framework, we assessed 30-day EQ-5D scores with the use of a linear regression model with indicators for treatment group, as well as for recruitment site and appendicolith status (randomization stratification factors). Our primary analysis included participants who completed all items on the 30-day EQ-5D survey. The estimated treatment effect and 97.5% one-sided confidence interval were analyzed with the use of a prespecified noninferiority margin of −0.05 points.[22] There was no adjustment for multiplicity in analyses of secondary outcomes, and these analyses should be considered exploratory. Details regarding stopping rules are provided in the Supplementary Appendix. An independent data and safety monitoring board reviewed three formal interim analyses, which were performed annually over the course of the trial, and did not recommend stopping the trial. To address potential selection bias, we performed a secondary

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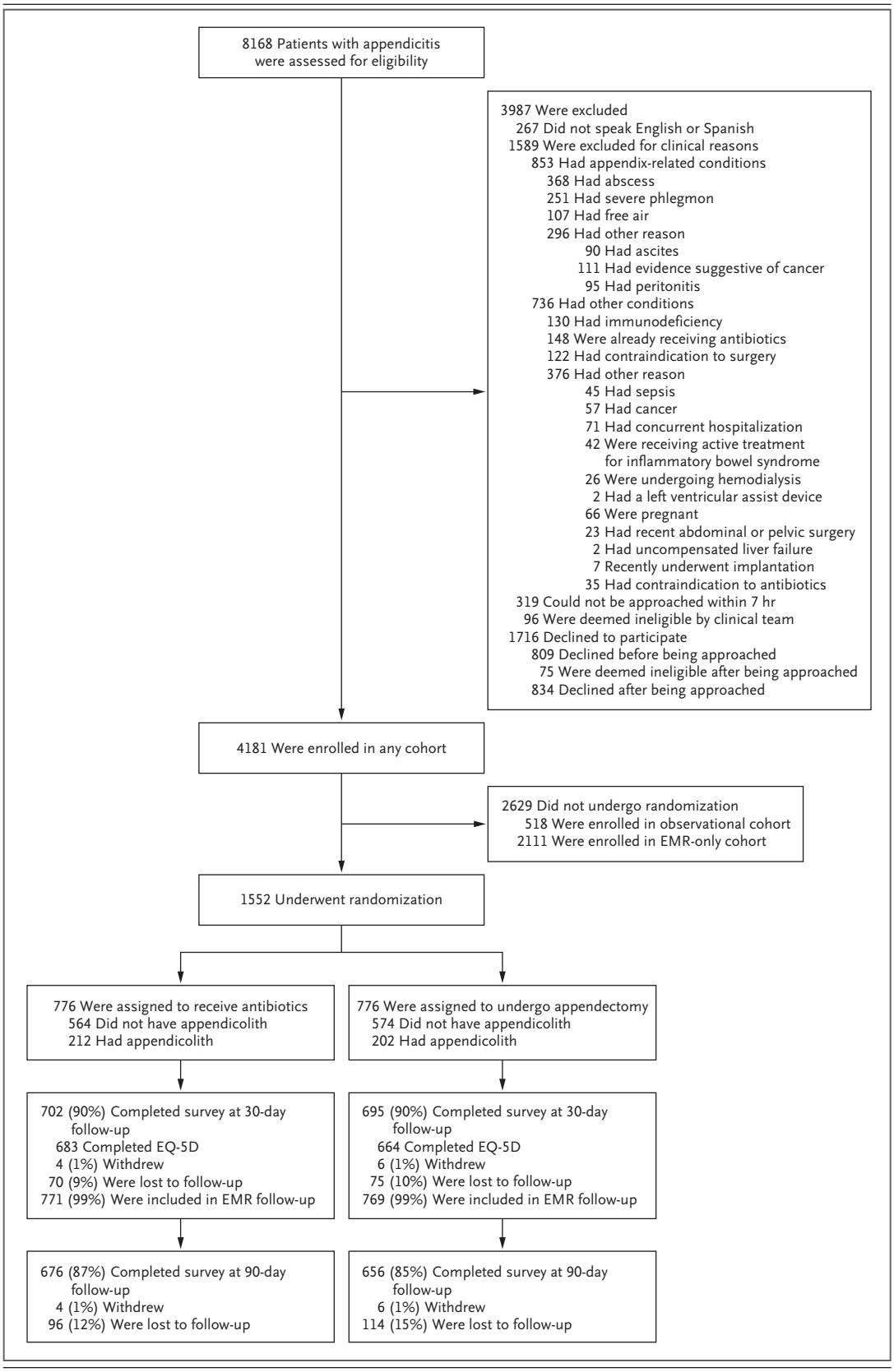
8168 Patients with appendicitis were assessed for eligibility
3987 Were excluded
267 Did not speak English or Spanish
1589 Were excluded for clinical reasons
853 Had appendix-related conditions
368 Had abscess
251 Had severe phlegmon
107 Had free air
296 Had other reason
90 Had ascites
111 Had evidence suggestive of cancer
95 Had peritonitis
736 Had other conditions
130 Had immunodeficiency
148 Were already receiving antibiotics
122 Had contraindication to surgery
376 Had other reason
45 Had sepsis
57 Had cancer
71 Had concurrent hospitalization
42 Were receiving active treatment for inflammatory bowel syndrome
26 Were undergoing hemodialysis
2 Had a left ventricular assist device
66 Were pregnant
23 Had recent abdominal or pelvic surgery
2 Had uncompensated liver failure
7 Recently underwent implantation
35 Had contraindication to antibiotics
319 Could not be approached within 7 hr
96 Were deemed ineligible by clinical team
1716 Declined to participate
809 Declined before being approached
75 Were deemed ineligible after being approached
834 Declined after being approached
4181 Were enrolled in any cohort
2629 Did not undergo randomization
518 Were enrolled in observational cohort
2111 Were enrolled in EMR-only cohort
1552 Underwent randomization
776 Were assigned to receive antibiotics
564 Did not have appendicolith
212 Had appendicolith
776 Were assigned to undergo appendectomy
574 Did not have appendicolith
202 Had appendicolith
702 (90%) Completed survey at 30-day follow-up
683 Completed EQ-5D
4 (1%) Withdrew
70 (9%) Were lost to follow-up
771 (99%) Were included in EMR follow-up
695 (90%) Completed survey at 30-day follow-up
664 Completed EQ-5D
6 (1%) Withdrew
75 (10%) Were lost to follow-up
769 (99%) Were included in EMR follow-up
676 (87%) Completed survey at 90-day follow-up
4 (1%) Withdrew
96 (12%) Were lost to follow-up
656 (85%) Completed survey at 90-day follow-up
6 (1%) Withdrew
114 (15%) Were lost to follow-up

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Figure 1 (facing page). Screening, Enrollment, Randomization, and Follow-up.

Patients could have more than one exclusion criterion. The patient surveys and timing of the study were the same for the observational cohort and the randomized cohort. The electronic medical record (EMR)–only cohort includes medical record data from the index hospitalization and 4-week and 2-year chart reviews. EQ-5D denotes European Quality of Life–5 Dimensions.

per-protocol analysis of EQ-5D scores and serious adverse events at 30 days. (Details regarding the interim and per-protocol analyses are provided in the Supplementary Appendix.) With adjustment for treatment group, recruitment site, and appendicolith status (if appropriate), binomial regression with a log link was used to calculate relative risks for binary outcomes, Poisson regression with robust standard errors was used to calculate rate ratios for count data, and linear regression was used for continuous outcomes. Effect sizes and corresponding 95% confidence intervals are presented for all comparisons. A Kaplan–Meier cumulative incidence curve was used to describe the incidence of appendectomy over time in the antibiotics group, both overall and according to appendicolith status. Data are current as of June 4, 2020 (the final day of the 90-day survey window for the last patient). All analyses were performed with the use of R statistical software, version 3.5.0 (R Foundation for Statistical Computing).

RESULTS

POPULATION

From May 3, 2016, through February 5, 2020, a total of 8168 patients underwent screening, of whom 1589 (19%) were ineligible for enrollment in the trial for clinical or appendicitis-related reasons (Fig. 1). A total of 1552 participants (31% of the patients who were eligible) underwent randomization; 776 were assigned to receive antibiotics, and 776 to undergo appendectomy (Table S2). Sociodemographic and clinical characteristics of the participants were similar in the two groups (Table 1 and Table S3). Imaging to confirm appendicitis was computed tomography (CT) alone or in combination with ultrasonography or magnetic resonance imaging in 96% of the participants. An appendicolith was found on imaging in 27% of the participants.

In the antibiotics group, 51% of the participants were admitted to the hospital for the index treatment, whereas 47% (range across sites, 0 to 81%) were discharged from the emergency department to home, of whom 79% were discharged within 24 hours after randomization; the remaining 2% had another discharge disposition (e.g., were in the observational unit). In the appendectomy group, 95% of the participants were admitted to the hospital for the index treatment, and 96% of the appendectomy procedures were performed laparoscopically. The mean time from randomization to discharge from either the emergency department or the hospital for the index treatment was 1.33 days in the antibiotics group and 1.30 days in the appendectomy group (Table 2). At least one additional course of antibiotics was prescribed within 90 days after the index treatment in 73 of 676 participants (11%) in the antibiotics group with 90-day follow-up data. Adherence to the treatment, as reported by sites, was 90% among participants in the antibiotics group and more than 99% among those in the appendectomy group.

PRIMARY AND SECONDARY CLINICAL OUTCOMES

The primary outcome, the mean 30-day EQ-5D score, was 0.92±0.13 in the antibiotics group and 0.91±0.13 in the appendectomy group (difference, 0.01 points; 95% confidence interval [CI], −0.001 to 0.03); these findings are consistent with noninferiority of antibiotics to appendectomy. Results were similar in the per-protocol analysis (difference, 0.01 points; 95% CI, −0.002 to 0.03) and in an analysis performed with the use of multiple imputation for missing primary-outcome data (difference, 0.01 points; 95% CI, −0.004 to 0.02).

Results in subgroups of participants with an appendicolith and those without an appendicolith also showed noninferiority of antibiotics with respect to the primary outcome (Table 2). In the antibiotics group, appendectomy had been performed in 11% of the participants by 48 hours, in 20% by 30 days, and in 29% by 90 days (Fig. 2); the 90-day incidence of appendectomy was 41% among those with an appendicolith and 25% among those without an appendicolith. Table 2 shows results for additional secondary outcomes, both overall and according to appendicolith status. The percentage of participants who had resolution of symptoms (i.e., the ab-

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Table 1. Sociodemographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Antibiotics (N=776)	Appendectomy (N=776)
Age — yr	38.3±13.4	37.8±13.7
Sex — no. (%)		
Female	286 (37)	290 (37)
Male	490 (63)	486 (63)
Gender different from sex assigned at birth — no. (%)	8 (1)	6 (1)
Race or ethnic group — no. (%)†		
White	461 (60)	449 (59)
Black	75 (10)	63 (8)
American Indian or Alaska Native	13 (2)	9 (1)
Asian	39 (5)	53 (7)
Native Hawaiian or Pacific Islander	4 (1)	3 (<1)
Multiple or other	176 (23)	185 (24)
Hispanic ethnic group†	362 (47)	366 (47)
Primary language — no. (%)		
English	469 (60)	464 (60)
Spanish	267 (34)	267 (34)
Other	40 (5)	45 (6)
Insurance — no. (%)		
Commercial	323 (43)	317 (42)
Medicare or Tricare	89 (12)	89 (12)
Medicaid or other state program	134 (18)	131 (17)
Other or no coverage	213 (28)	217 (29)
Modified Charlson comorbidity index score‡	0.24±0.53	0.24±0.53
Body-mass index§	29.0±6.6	28.6±6.1
Duration of symptoms — days	1.8±3.6	1.6±1.6
Alvarado score¶	6.6±1.6	6.7±1.7
History of fever — no. (%)	194 (25)	185 (24)
Initial white-cell count — per μl	12,900±4000	13,400±4100
Imaging test — no. (%)		
Computed tomography alone	626 (81)	609 (78)
Ultrasonography alone	24 (3)	30 (4)
>1 Imaging test	125 (16)	137 (18)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. Data were missing for 26 participants in the antibiotics group and 30 participants in the appendectomy group for gender different from sex assigned at birth; 8 and 14 participants, respectively, for race or ethnic group; 17 and 22 for insurance; 3 and 2 for modified Charlson comorbidity index score; 209 and 104 for body-mass index; 1 and 1 for duration of symptoms; 38 and 38 for Alvarado score; 0 and 1 for history of fever; and 3 and 1 for initial white-cell count. Additional information regarding patient characteristics is provided in Table S3.

† Race and ethnic group were reported by the participant. If the participant did not report the information and it was listed in the participant's chart, the information from the chart was used.

‡ Scores on the modified Charlson comorbidity index range from 0 to 40, with lower scores indicating fewer coexisting conditions and a lower short-term risk of death.

§ Body-mass index is the weight in kilograms divided by the square of the height in meters.

¶ Alvarado scores range from 0 to 10, with higher scores indicating a higher likelihood of having appendicitis.

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sence of pain, tenderness, and fever) was similar in the two groups by 7, 14, and 30 days. The percentage with a visit to the emergency department or urgent care clinic after the index treatment was 9% in the antibiotics group and 4% in the appendectomy group, and the percentage with any hospitalization after the index treatment (including for eventual appendectomy) was 24% and 5%, respectively. The mean number of missed work days for participants was 5.26 in the antibiotics group and 8.73 in the appendectomy group, and the mean number of missed work days for caregivers was 1.33 and 2.04, respectively. Appendiceal neoplasms were identified in nine participants (mean age, 47±17 years; range, 21 to 74) — seven in the appendectomy group and two in the antibiotics group who had undergone appendectomy. Eight of the neoplasms were carcinomas, and one was a mucocele.

ADVERSE EVENTS

There were no deaths (Table 3 and Table S4). The rate of serious adverse events was 4.0 per 100 participants in the antibiotics group and 3.0 per 100 participants in the appendectomy group (rate ratio, 1.29; 95% CI, 0.67 to 2.50). The rate of NSQIP-defined complications was 8.1 per 100 participants in the antibiotics group and 3.5 per 100 participants in the appendectomy group (rate ratio, 2.28; 95% CI, 1.30 to 3.98), and at least one such event occurred in 5% and 3% of the participants, respectively. The higher rate in the antibiotics group overall was attributable to those with an appendicolith (20.2 vs. 3.6 per 100 participants) and not to those without an appendicolith (3.7 vs. 3.5 per 100 participants). The rate of site-related infectious complications (incisional or organ–space infections) was also higher among those with an appendicolith. Percutaneous drainage procedures were more common in the antibiotics group than in the appendectomy group overall (2.5 vs. 0.5 per 100 participants; rate ratio, 5.36; 95% CI, 1.55 to 18.50) and particularly among those with an appendicolith. Reactions to antibiotics that led to a health care encounter were more common in the antibiotics group than in the appendectomy group (3.3 vs. 0.2 per 100 participants), with one reaction in the antibiotics group classified as life-threatening. The rate of *C. difficile* infection was 0.6 per 100 participants in the two groups.

Identification of an appendiceal perforation during an operation or on pathological review was less common in the antibiotics group than in the appendectomy group (occurring in 9% vs. 15% of the participants), but the majority of participants in the antibiotics group did not have surgery and thus could not be assessed. When the analysis was limited to participants in either group who had undergone appendectomy, the percentage with a perforation was higher in the antibiotics group than in the appendectomy group (32% vs. 16%); the higher rate in the antibiotics group overall was attributable to those with an appendicolith (61% vs. 24%) and not to those without an appendicolith (14% vs. 13%). The rate of use of more extensive procedures (small-bowel or colon resection, reoperation, laparotomy, colostomy, or ileostomy) was low and similar in the two groups (1.0 vs. 0.8 per 100 participants).

DISCUSSION

In this large, randomized trial of antibiotics for appendicitis, antibiotics were noninferior to appendectomy on the basis of results of a commonly used measure of health status at 30 days. By 90 days, 29% of the participants in the antibiotics group had undergone appendectomy, including 41% of those with an appendicolith and 25% of those without an appendicolith. NSQIP-defined complications were more common in the antibiotics group than in the appendectomy group but were attributable to participants with an appendicolith, who additionally appeared to have a higher risk of serious adverse events than those without an appendicolith. By 1 week, resolution of symptoms of appendicitis was similar in the two groups. Nearly half the participants assigned to receive antibiotics were not hospitalized for the index treatment. Participants and their caregivers in the antibiotics group missed less time from work than those in the appendectomy group, but emergency department visits and hospitalizations after the index treatment were more common in the antibiotics group.

The EQ-5D score at 30 days was selected as the primary outcome because it is a validated measure of overall health status responsive to appendicitis treatment,[21] and the time period is typical for recovery from appendectomy. Numer-

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Table 2. Intention-to-Treat Comparison of Patient-Reported Outcomes, Clinical Outcomes, Time Spent in Health Care Settings, and Missed Work.*

Outcome	Overall			Appendicolith Present			Appendicolith Absent		
	Antibiotics	Surgery	Effect (95% CI)	Antibiotics	Surgery	Effect (95% CI)	Antibiotics	Surgery	Effect (95% CI)
EQ-5D at 30 days†‡	0.92±0.13	0.91±0.13	0.01 (−0.001 to 0.03)§	0.92±0.14	0.92±0.13	−0.01 (−0.03 to 0.02)§	0.92±0.13	0.91±0.13	0.02 (0.003 to 0.03)§
Resolution of symptoms — no./total no. (%)¶‖									
By 7 days	350/714 (49)	344/688 (50)	0.99 (0.89 to 1.10)**	71/189 (38)	85/183 (46)	0.81 (0.64 to 1.03)**	279/525 (53)	259/505 (51)	1.04 (0.92 to 1.16)**
By 14 days	446/685 (65)	435/678 (64)	1.02 (0.94 to 1.10)**	103/182 (57)	102/176 (58)	0.98 (0.82 to 1.18)**	343/503 (68)	333/502 (66)	1.03 (0.94 to 1.12)**
By 30 days	462/676 (68)	466/663 (70)	0.97 (0.91 to 1.04)**	125/180 (69)	111/163 (68)	1.02 (0.88 to 1.18)**	337/496 (68)	355/500 (71)	0.96 (0.88 to 1.04)**
Days from randomization to discharge for index treatment — no. of days/no. of participants (mean)‡	1030/776 (1.33)	1010/776 (1.30)	1.00 (0.89 to 1.13)††	403/212 (1.90)	330/202 (1.63)	1.15 (0.89 to 1.47)††	626/564 (1.11)	679/574 (1.18)	0.92 (0.82 to 1.05)††
Any hospitalization after index treatment within 90 days — no./total no. (%)‖	154/635 (24)	32/613 (5)	4.62 (3.21 to 6.65)**	57/176 (32)	8/157 (5)	6.36 (3.13 to 12.90)**	97/459 (21)	24/456 (5)	4.02 (2.62 to 6.16)**
Days in hospital after index treatment within 90 days — no. of days/no. of participants (mean)‡	421/622 (0.68)	93/609 (0.15)	4.38 (2.49 to 7.73)††	191/166 (1.15)	37/156 (0.24)	4.55 (1.46 to 14.18)††	230/456 (0.50)	56/453 (0.12)	4.07 (2.24 to 7.41)††
Any visit to emergency department or urgent care clinic after index treatment within 90 days — no./total no. (%)‖	55/618 (9)	26/604 (4)	2.07 (1.32 to 3.25)**	14/165 (8)	2/153 (1)	6.49 (1.50 to 28.09)**	41/453 (9)	24/451 (5)	1.70 (1.05 to 2.77)**
Visits to emergency department or urgent care clinic after index treatment within 90 days — no. of visits/no. of participants (mean)‡	66/615 (0.11)	24/599 (0.04)	2.64 (1.57 to 4.43)††	17/163 (0.10)	2/153 (0.01)	8.19 (2.03 to 33.00)††	49/452 (0.11)	22/446 (0.05)	2.15 (1.23 to 3.76)††
Days of missed work for participant within 90 days — no. of days/no. of participants (mean)‡	2516/478 (5.26)	4131/473 (8.73)	0.63 (0.51 to 0.77)††	743/121 (6.14)	1134/125 (9.07)	0.72 (0.48 to 1.09)††	1773/357 (4.97)	2997/348 (8.61)	0.60 (0.48 to 0.76)††
Days of missed work for caregiver within 90 days — no. of days/no. of caregivers (mean)‡	679/509 (1.33)	1009/495 (2.04)	0.66 (0.48 to 0.91)††	242/137 (1.77)	213/126 (1.69)	1.04 (0.56 to 1.92)††	437/372 (1.17)	796/369 (2.16)	0.56 (0.38 to 0.82)††

* Plus–minus values are means ±SD. Confidence intervals for secondary outcomes and subgroup analyses were not adjusted for multiple comparisons; thus, they are exploratory and should not be used to infer definitive treatment effects.

† Scores on the European Quality of Life–5 Dimensions (EQ-5D) questionnaire range from 0 to 1, with higher scores indicating better health status; the minimal clinically important difference is 0.05 points.

‡ The overall analysis was adjusted for recruitment site and appendicolith status, and the subgroup analyses were adjusted for recruitment site.

§ The effect is a mean difference.

¶ Resolution of symptoms was defined as the absence of pain, tenderness, and fever.

‖ The overall analysis was adjusted for appendicolith status, and the subgroup analyses were unadjusted.

** The effect is a relative risk.

†† The effect is a rate ratio.

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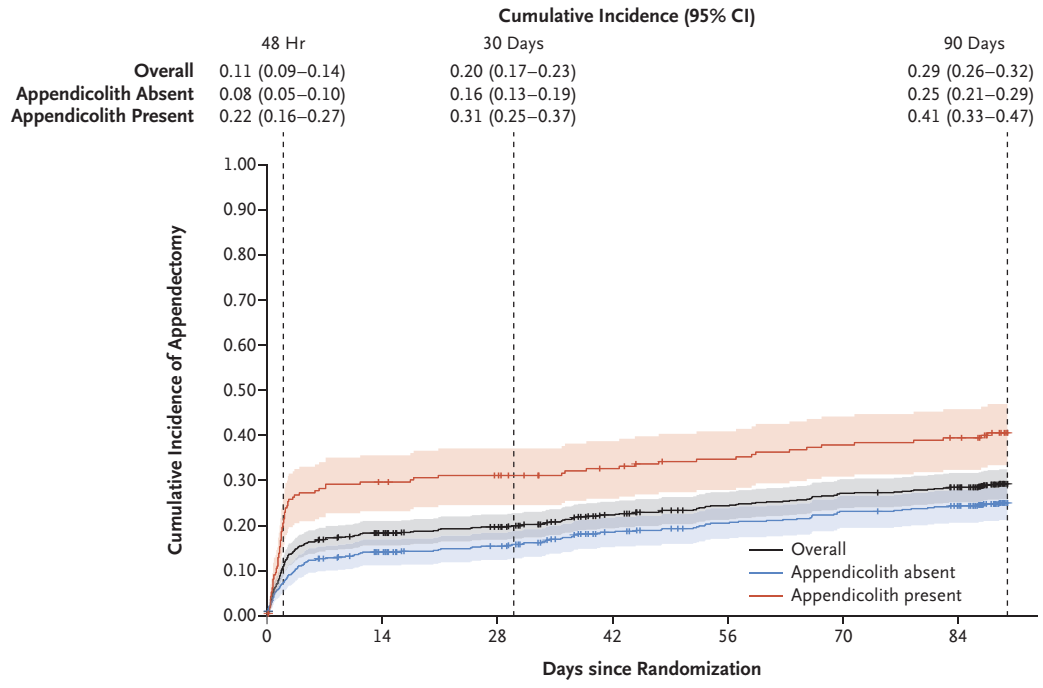

No. at Risk							
Overall	776	616	589	542	518	499	485
Appendicolith absent	564	470	448	411	394	381	371
Appendicolith present	212	146	141	131	124	118	114

Cumulative No. of Events							
Overall	0	141	151	170	184	203	212
Appendicolith absent	0	79	86	102	112	125	131
Appendicolith present	0	62	65	68	72	78	81

Figure 2. Cumulative Incidence of Appendectomy in the Antibiotics Group.
Plus signs indicate censoring because the participant withdrew or was lost to follow-up.

ous secondary outcomes — including appendectomy (if the participant was initially treated with antibiotics), complications, time spent in health care settings, and missed work — are also recognized as important considerations in decision making. Another relevant outcome is the potential for missed neoplasm in patients who are not undergoing appendectomy. Although almost all participants underwent CT, and those with evidence suggestive of a mass were excluded, nine neoplasms were identified in the appendectomy specimens. Of note, fewer neoplasms were found among participants in the antibiotics group, and it is unknown whether earlier detection affected patient outcomes.

The CODA trial enrolled patients who had more severe appendicitis than patients in previous trials and included those with an appendicolith. Although appendicoliths are commonly identified on CT and are found in approximately 20% of pathological specimens from patients with and without appendicitis,[23] their effect on treatment success is unclear. Appendicoliths have been linked to a higher rate of complicated appendicitis,[24-26] so patients with an appendicolith were included in a prespecified subgroup in our trial. The broad inclusion criteria of the CODA trial may in part explain the differences in outcomes between our trial and the Appendicitis Acuta (APPAC) trial, the largest previous randomized trial addressing this question (with 530 total patients).[7] The APPAC trial excluded patients with an appendicolith and approached only 30% of all patients with appendicitis. In the APPAC trial, the incidence of appendectomy in the antibiotics group was 16% at 90 days (Salminen P:

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Table 3. Adverse Events and Complications at 90 Days.*

Event	Overall			Appendicolith Present			Appendicolith Absent		
	Antibiotics	Surgery	Effect (95% CI)†	Antibiotics	Surgery	Effect (95% CI)†	Antibiotics	Surgery	Effect (95% CI)†
Serious adverse events									
Participants with ≥1 event — no./total no. (%)	19/676 (3)	19/656 (3)	0.97 (0.52 to 1.80)	11/183 (6)	6/169 (4)	1.69 (0.64 to 4.48)	8/493 (2)	13/487 (3)	0.61 (0.25 to 1.45)
Total events — no. of events/no. of participants (events per 100 participants)	27/676 (4.0)	20/656 (3.0)	1.29 (0.67 to 2.50)	17/183 (9.3)	6/169 (3.6)	2.62 (0.95 to 7.24)	10/493 (2.0)	14/487 (2.9)	0.71 (0.28 to 1.76)
Unplanned hospitalization not for appendectomy	19/676 (2.8)	19/656 (2.9)	0.96 (0.48 to 1.91)	10/183 (5.5)	6/169 (3.6)	1.54 (0.55 to 4.30)	9/493 (1.8)	13/487 (2.7)	0.68 (0.26 to 1.80)
NSQIP-defined complications‡									
Participants with ≥1 event — no./total no. (%)	37/676 (5)	21/656 (3)	1.72 (1.02 to 2.90)	26/183 (14)	5/169 (3)	4.80 (1.89 to 12.22)	11/493 (2)	16/487 (3)	0.68 (0.32 to 1.45)
Total events — no. of events/no. of participants (events per 100 participants)	55/676 (8.1)	23/656 (3.5)	2.28 (1.30 to 3.98)	37/183 (20.2)	6/169 (3.6)	5.69 (2.11 to 15.38)	18/493 (3.7)	17/487 (3.5)	1.05 (0.45 to 2.43)
Site-related infectious complication§	33/771 (4.3)	21/769 (2.7)	1.54 (0.87 to 2.72)	22/210 (10.5)	7/200 (3.5)	2.99 (1.30 to 6.92)	11/561 (2.0)	14/569 (2.5)	0.80 (0.33 to 1.92)
Drainage procedure	17/676 (2.5)	3/656 (0.5)	5.36 (1.55 to 18.50)	12/183 (6.6)	1/169 (0.6)	11.08 (1.42 to 86.55)	5/493 (1.0)	2/487 (0.4)	2.47 (0.48 to 12.67)
Reaction to antibiotics that led to a health care encounter — no. of events/no. of participants (events per 100 participants)	22/676 (3.3)	1/656 (0.2)	21.36 (2.86 to 159.67)	6/183 (3.3)	0/169	NA	16/493 (3.2)	1/487 (0.2)	15.81 (2.07 to 120.50)
Clostridioides difficile colitis — no. of events/no. of participants (events per 100 participants)	4/676 (0.6)	4/656 (0.6)	0.99 (0.21 to 4.63)	0/183	0/169	NA	4/493 (0.8)	4/487 (0.8)	0.99 (0.21 to 4.63)

* All overall analyses were adjusted for appendicolith status, and all subgroup analyses were unadjusted. NA denotes not applicable.
† The effect is a relative risk for participants with ≥1 event and is a rate ratio for all other outcomes.
‡ Individual frequencies for National Surgical Quality Improvement Program (NSQIP)–defined complications are provided in Table S4.
§ Site-related infectious complications were defined as incisional infections or organ–space infections (abscesses) that had occurred at 30 days.

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personal communication), 27% at 1 year, and 39% at 5 years.[27] The percentage of patients who were found to have a perforation during the index appendectomy procedure was less than 2% in the APPAC trial,[7] as compared with 16% in the appendectomy group in the CODA trial (13% among those without an appendicolith), a finding consistent with the greater severity of appendicitis in our trial population. The rate of perforation identified in the CODA trial is consistent with rates reported in population studies of appendicitis.[28] Disease severity, particularly related to the presence of an appendicolith, may have also contributed to our finding of a higher risk of abscess formation and drainage procedures in the antibiotics group, although these were uncommon events. In our trial, most appendectomy procedures were laparoscopic and nearly half the participants in the antibiotics group received the antibiotics in the emergency department (avoiding hospitalization for the index treatment), whereas in the APPAC trial, surgeons used only open surgical techniques and hospital stays were required in both treatment groups. These differences probably explain the higher observed rate of site-related infectious complications in the appendectomy group and the longer hospitalizations in both treatment groups in the APPAC trial than in the CODA trial.[7] Of note, both trials showed that missed work was less frequent in the antibiotics group. A recent meta-analysis of five randomized trials showed lower complication rates and shorter disability with antibiotic treatment than with appendectomy.[29]

This report has the following limitations. It includes only 90-day follow-up data and thus underrepresents recurrence and long-term complications; ongoing follow-up will inform longer-term outcomes. Although almost all patients with appendicitis were approached for participation in the trial, only approximately 30% of eligible patients agreed to undergo randomization, with variation in this percentage across sites, and this factor may have introduced selection bias; a parallel observational cohort study that includes approximately 500 patients who selected their treatment is currently ongoing. Because this was a pragmatic trial, the protocol did not specify requirements for hospitalization or for a given antibiotic regimen. The trial was not blinded, and this factor may have influenced several outcomes, including the primary outcome. In addition, some patients in the appendectomy group declined surgery, and some patients in the antibiotics group underwent appendectomy without meeting protocol-specified criteria for surgery. In a small previous study, Talan et al.[30] found that outpatient management was feasible. In the CODA trial, patients were selected to receive antibiotics on an outpatient basis according to protocol-specified discharge criteria, and rates of use varied greatly across sites. Because of expected confounding related to site and patient characteristics, we did not assess outcomes according to outpatient or inpatient treatment. Although we prespecified a plan to assess outcomes according to the presence or absence of an appendicolith, our observations in these subgroups must be considered in the context of the small numbers of several individual complications. Furthermore, there was no adjustment for multiple testing of secondary outcomes.

This comparative effectiveness trial showed that, for the treatment of appendicitis, antibiotics were noninferior to appendectomy on the basis of results of a standardized measure of general health status, at least in the short term. In the antibiotics group, nearly 3 in 10 participants had undergone appendectomy by 90 days, and there were more emergency department visits and hospitalizations after the index treatment than in the appendectomy group. An alternative perspective is that, in the antibiotics group, more than 7 in 10 participants avoided surgery, many were treated on an outpatient basis, and participants and caregivers missed less time at work than with appendectomy. In the antibiotics group, participants with an appendicolith were at a higher risk for both appendectomy and complications than participants without an appendicolith. These data may be particularly relevant during the Covid-19 pandemic, as patients and clinicians weigh the benefits and risks of each approach, considering individual characteristics, preferences, and circumstances.

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APPENDIX

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